REMARKS

A check for the fees for a two-month extension of time and for filing an RCE accompanies this response. A request for Continued Examination and an Information Disclosure Statement also accompany this paper. Any fee that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 06-1050.

Claims 1, 2, 4-10, 18, 19, 50-55, 59-61, 65-72 and 117-122 are pending in this application. Claims 73-116, which are withdrawn from consideration as being drawn to non-elected subject matter, are retained for possible rejoinder. Applicant wishes to point out that claim 18 was amended and listed as such in the claim list of the Response submitted June 17, 2004. The amendment to claim 18, however, was inadvertently left out of the remarks section and header of the claim list. Applicant also notes that in the instant Office Action claim 18 was not acknowledged as amended. For clarity, Applicant has presented the same amendments herein and marked claim 18 again as "currently amended."

Claim 4 is amended for clarity to render it clear that the claimed polypeptide contains an MTSP7 portion that is a protease domain of MTSP7 and the specified MTSP7 portion is the only MTSP7 portion of the polypeptide, so that the claimed polypeptide cannot and does not read on a full-length MTSP7 polypeptide. The claim also is amended to render it clear that the protease domain of MTSP7 is selected from among the listed alternatives a) b) and c). Hence, claim 4 does not encompass full-length MTSP7 polypeptides, nor polypeptides that contain additional regions of MTSP7 other than the protease domain. Basis for this amendment can be found, for example, at page 28, lines 19-23. Claim 18 is amended to depend from claim 1. Basis for this amendment can be found for example at page 9, lines 1-9. Claims 65 and 69 are amended to recite that the identified compounds of the method inhibit tumorigenesis. Basis for this amendment cab be found for example, at page 6, lines 4-12 and at page 86, line 7 to page 87, line 14. Therefore no new matter is added.

I. CLAIM REJECTIONS UNDER 35 U.S.C. §101

Claims 65-67 and 69-72 are rejected under 35 U.S.C. §101 as allegedly lacking patentable utility for reasons of record. In particular, it is alleged that that the instant application cannot identify any specific, substantial utility for any modulator that might be

identified by methods known to the inventors at the time the application was filed. It is further alleged that Applicant has failed to establish that a product found by the claimed methods can have any substantial and specific effect on the protease itself because the public cannot know how to use modulators identified by a claimed assay to achieve a specific or substantial alteration of the unknown, native proteolytic activity of the disclosed MTSP7 protease. Further, with respect to a proposed diagnostic utility, it is alleged that since claims pertaining to methods that identify molecules that bind to MTSP7 were not elected and the instant claims do not require binding, such utility can not be asserted for the instant claims. It is alleged that diagnostic utilities argued in the previous response do not specify a specific disease or condition. Therefore, it is alleged that there is no specific utility for the products of the claimed methods and thus, there is no specific utility for the claimed methods.
In light of the amendments herein and remarks below, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Relevant Law

It is common and sensible for an applicant to identify several specific utilities for an invention, particularly where the invention is a product (e.g., a machine, an article of manufacture or a composition of matter). Regardless of the category of invention that is claimed (*e.g.*, product or process), an applicant need only make one credible assertion of specific utility to satisfy 35 U.S.C. §101 and 35 U.S.C. §112; additional statements of utility, even if not "credible," do not render the claimed invention lacking in utility. *See, e.g.*, Raytheon v. Roper, 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. §101 is clearly shown."); In re Gottlieb, 328 F.2d 1016, 1019, 140 USPQ 665, 668 (CCPA 1964) ("Having found that the antibiotic is useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification as possibly useful."); In re Malachowski, 530 F.2d 1402, 189 USPQ 432 (CCPA 1976); Hoffman v. Klaus, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988). Thus, if applicant makes one credible assertion of utility, utility for the claimed invention as a whole is established.

The MPEP provides further guidance to its office personnel that: Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar

formulations in other cases to mean that products or services based on the claimed subject matter must be "currently available" to the public in order to satisfy the utility requirement. *See, e.g.*, Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

In addition, rejections under 35 U.S.C. §101 rarely have been sustained by federal courts. Generally speaking, in these rare cases, the 35 U.S.C. §101 rejection was sustained either because the applicant failed to disclose any utility or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. In re Gazave, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967).

ANALYSIS

The claims at issue are directed to methods of identifying compounds that modulate the protease activity of a polypeptide by contacting a polypeptide of claims 1 or 4 with a substrate that is proteolytically cleaved by the polypeptide, and, either simultaneously, before or after, adding a test compound or plurality thereof. The amount of substrate cleaved in the presence of the test compound is measured and compounds are selected that change the amount of substrate cleaved compared to a control, whereby compounds that modulate the activity of the polypeptide are identified. The instant claims also specify that the identified compounds inhibit tumorigenesis.

Inhibiting tumorigenesis by modulating an MTSP7 protease is a specific, substantial and credible utility for the products identified by the methods and hence, a specific, substantial and credible utility for the methods themselves. As the specification explains neoplastic diseases proliferate by the generation, increase and metastasis of a tumor mass. Cells that acquire such phenotypes often activate new genes and biochemical functions that are inactive or present at different levels in non-tumor cells (see for example, at pages 1-2). Proteases, especially cell surface proteases are implicated in tumorigenesis because one of the hallmarks of tumorigenesis is the breakdown of the basement membrane by proteolytic and other enzymes (see for example, at page 2).

MTSP7 is a transmembrane protein with an extracellular protease domain that can play a role in proteolytic degradation at the cell surface as well as signal transduction (see for example, at page 4, lines 12-24 and at page 47, lines 16-29). The specification further explains that MTSP7 levels differ in tumor and non-tumor cells (page 11, lines 5-12):

> MTSPs are of interest because they appear to be expressed and/or activated at different levels in tumor cells from normal cells, or have functional activity that is different in tumor cells from normal cells, such as by an alteration in a substrate therefor, or a cofactor. MTSP7 is of interest because it is expressed or is active in tumor cells.

The specification states that the level of activated MTSP7 can be diagnostic of cervical or lung cancer or leukemia (see above). The specification explains that MTSPs such as MTSP7 therefore are therapeutic targets (page 47, line 16 to page 48, line 2):

> The MTSP family is a target for therapeutic intervention and also some members can serve as diagnostic markers for tumor development, growth and/or progression. As discussed, the members of this family are involved in proteolytic processes that are implicated in tumor development, growth and/or progression. This implication is based upon their functions as proteolytic enzymes in processes related to ECM degradative pathways. In addition, their levels of expression or level of activation or their apparent activity resulting from substrate levels or alterations in substrates and levels thereof differs in tumor cells and non-tumor cells in the same tissue. Hence, protocols and treatments that alter their activity, such as their proteolytic activities and roles in signal transduction, and/or their expression, such as by contacting them with a compound that modulates their activity and/or expression, could impact tumor development, growth and/or progression. Also, in some instances, the level of activation and/or expression can be altered in tumors, such as lung carcinoma, colon adenocarcinoma and ovarian carcinoma.

The specification describes methods of identifying compounds that modulate MTSP7. For example, at pages 70-71 the specification explains that the screening methods can be employed to identify compounds that inhibit MTSP7 proteolytic activity in tumor cells where MTSP7 is expressed at high levels and that compounds that enhance MTSP7 proteolytic activity in tumor cells can be identified where MTSP7 is expressed at low levels. The specification explains that such compounds can be used in cancer treatments. The specification then details the screening assays as instantly claimed. Further, the specification explains that compounds identified by such screening methods can be further selected to inhibit tumorigenesis. At pages 86-87, the specification describes several *in vivo* and animal model assays for inhibiting tumorigenesis. For example, an assay to evaluate the activity of a compound to reduce tumor growth through inhibition of MTSP7 protein is described. Cell

lines are injected into SCID mice to establish tumors. After tumors are established, the mice are given test compound and tumor volume is monitored to identify compounds that inhibit tumor growth. The specification also describes additional assays including an assay to evaluate the inhibition and reduction of tumor metastasis in mouse lung colonization and dosing assays to assess decreases in tumor volume and metastasis in animal models. In addition, the specification further describes that compounds identified in the described screening methods can be used to treat neoplastic diseases (page 129, lines 24-28).

Hence, the specification provides methods for identifying compounds that modulate MTSP7. The specification shows that such compounds are candidates as inhibitors of tumorogenesis. The specification explains that the products of the methods can be used to inhibit tumorogenesis in treatments of neoplastic diseases. Thus, the products of the methods have a utility in the treatment of neoplastic diseases through the specific modulation of MTSP7 which thereby inhibits tumorigenesis. Therefore, those of skill in the art would recognize that identified compounds have a specific, substantial and credible utility. Moreover, one of skill in the art would recognize that the instantly claimed methods, directed to methods of identifying such compounds, therefore provide a specific, substantial and credible utility. Applicant respectfully requests withdrawal of the rejection.

II. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112 FIRST PARAGRAPH

A. The written description rejection of claims 1, 2, 4-6, 9, 10, 18, 19, 50-55, 59-61, 65-67, 69-72, and 117-120

Claims 1, 2, 4-6, 9, 10, 18, 19, 50-55, 59-61, 65-67, 69-72, and 117-120 are rejected under 35 U.S.C. §112, first paragraph because it is alleged that the specification does not describe the subject matter in such a way as to convey to one skilled in the relevant art that the inventor(s) had possession of the claimed subject matter at the time the application was filed. In particular, it is alleged that the specification does not exemplify, describe, suggest or otherwise discuss preparation of divergent proteases that include as many as 10% of the amino acid positions that differ from the MTSP7 polypeptides set forth in the application in SEQ ID NOS: 16 and 18. Responsive to Applicant's arguments, the instant Office Action urges that the specification only identifies the catalytic triad and a cysteine within the protease domain as identifying characteristics. Hence, it is alleged that identification of these features does not provide one of skill in the art sufficient guidence of the location or nature of

the modifications in the polypeptides to evidence possession of the polypeptides as claimed. This rejection is respectfully traversed.

The Claims

Claim 1 is directed to a substantially purified single or two chain MTSP7 polypeptide or a catalytically active portion of the polypeptide. The polypeptide is selected from among: a) a polypeptide that comprises a sequence of amino acids having at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16, and b) a polypeptide that comprises a sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 15. The polypeptide has serine protease activity.

Claim 4 is directed to a substantially purified single or two chain polypeptide that comprises an MTSP7 portion. The specified MTSP7 portion of the polypeptide is the only MTSP9 portion of the single or two chain polypeptide polypeptide. The MTSP7 portion is a protease domain of MTSP7 that is selected from the three listed alternatives: a) a polypeptide consisting essentially of the sequence of amino acids set forth as amino acids 206-438 in SEQ ID No. 16, b) a polypeptide consisting essentially of the sequence of amino acids that has at least about 90% amino acid sequence identity with the sequence of amino acids set forth as SEQ ID No. 18 and c) a polypeptide that is a catalytically active portion of a) or b). The MTSP7 portion of the polypeptide has serine protease activity. Hence, claim 4 does not read on full-length MTSP7 polypeptides.

Claims 119 and 120 are directed to substantially purified activated two chain polypeptides comprising the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a catalytically active portion thereof. The polypeptide has at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16 or 18, and the polypeptide has serine protease activity.

Claim 121 is directed to a substantially purified single or two chain polypeptide, comprising the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a catalytically active portion thereof, where the polypeptide has at least about 80% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16 and the polypeptide has serine protease activity. Claim 122 is directed to a substantially purified single or two chain polypeptide, consisting essentially of the protease domain of MTSP7 or a catalytically active portion thereof, where the protease domain or a catalytically active

portion thereof has at least about 80% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 18 and the polypeptide has serine protease activity.

SUMMARY OF POINTS ADDRESSED

Applicant respectfully submits that the instant application adequately describes the claimed polypeptides to demonstrate possession of the claimed subject matter at the time of the effective filing date of each claim. As is discussed in more detail below, to satisfy the written description requirement, one need not provide an example of every species encompassed by a claim. It is sufficient to provide identifying characteristics, including structural and physical characteristics, functional characteristics coupled with known or disclosed correlation with structural characteristics to demonstrate that the applicant was in possession of the claimed subject matter. MPEP § 2163; *see* University of California v. Eli Lilly, 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Further, the standard is an objective one, based on what one of skill in the art would recognize in the disclosure. In re Gosteli, 872 F.2d at 1012.

The discussion below addresses following in detail:

1. The specification defines and describes a genus of polypeptides sufficient to satisfy the written description requirement.

2. The specification provides identifying characteristics of MTSP7 polypeptides, including structural and physical characteristics of proteases and correlations between structural and functional characteristics that further demonstrate possession of the claimed polypeptides.

3. The level of knowledge with respect to serine proteases was exceptionally high as of the time of filing.

4. In light of the descriptions in the specification and the high level of knowledge in the art, one of skill in the art would recognize Applicant's possession of the claimed subject matter

Therefore, as demonstrated below, Applicant had possession of the claimed subject matter including polypeptides that have serine protease activity and have at least about 80% or 90% identity to SEQ ID NOS: 16 and 18, conjugates and solid supports comprising such polypeptides and methods of using such polypeptides as instantly claimed.

DETAILED ANALYSIS

1. The specification defines and describes a genus of polypeptides

An objective standard for determining whether a disclosure complies with the written description requirement is an affirmative answer to the query: "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed?" In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The instant specification defines a genus of polypeptides as claimed such that one of skill in the art would recognize that genus. Recognition thereof is sufficient to evidence applicant's possession of the claimed subject matter

A polypeptide having at least about 80% identity to a defined sequence, *e.g.* SEQ ID NOS; 16 or 18, or having at least about 90% identity to such sequences defines a genus of chemical entities that includes a defined number of polypeptides. The genus is defined and concrete based on this structural definition. The specification describes a genus that includes polypeptides with at least about 80% identity (or at least about 90% identity) to SEQ ID NOS: 16 and 18 that have serine protease activity (see for example, page 8, line 25-31, page 51, lines 5-10 and original claim 11). The specification describes polypeptides that consist essentially of an MTSP7 protease domain as well as polypeptides that encompass larger portions of MTSP7 polypeptides including the full-length sequence (see for example, page 49, lines 22-27 and page 52, lines 4-10). The specification provides the amino acid sequences of SEQ ID NOS: 16 and 18. The specification provides descriptions of how to assess identity and these techniques were well known in the art (see for example, page 24, line 16 to page 26, line 22).

In addition to the defined structural features, the specification describes structure-function relationships that identify the claimed genus of polypeptides having serine protease activity. Such description includes structural information, such as the presence of the catalytic triad of amino acid residues necessary for serine protease activity (for example, page 19, lines 5-8 and 16-18). The specification also provides an exemplary assay that demonstrates the serine protease activity of the genus of polypeptides (for example, Example 3, at page 160). As noted in the application, and known in the art, the presence of a catalytic triad confers serine protease activity. Hence, the identification of this feature is sufficient to identify a genus of polypeptides that have serine protease activity.

Therefore, the specification defines a genus of polypeptides that one of skill in the art could recognize. One of skill in the art using routine methods can clearly identify all of the polypeptides that possess at least about 80% sequence identity (or 90% identity) to the disclosed polypeptides and that possess serine protease activity as claimed. One of skill in the art can routinely identify the catalytic triad, a requisite structure feature necessary for serine protease activity. Hence, these characteristics sufficiently define the claimed genus to evidence possession of the claimed subject matter.

The Examiner cites University of California v. Eli Lilly, 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court stated in Eli Lilly that the written description requirement can be met by providing relevant identifying characteristics, including structural and physical characteristics, functional characteristics coupled with known or disclosed correlation with structural characteristics to demonstrate that the applicant was in possession of the claimed subject matter. Id. Applicant does not dispute this standard; this standard has been met. The structural features of the claimed sequence identity and the presence of serine protease activity defined by the presence of a catalytic triad, are sufficient features to evidence Applicant's possession of the claimed subject matter.

Additionally, in Eli Lilly the court stated:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

The court contrasted the subject matter at issue in that case with this statement by stating that the Applicant did not define which genes would fall into the genus labeled "vertebrate insulin cDNA" or "mammalian insulin cDNA." Id. The court stated that "[o]ne skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Id.

In comparison, the instant claims define chemical formulae with at least about 80% or 90 % identity to SEQ ID NO: 16 and 18 and require that the polypeptides have serine protease activity. Using such formulae, "[o]ne skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass." Id. One of skill in the art can visualize or recognize the identity of the members of the genus.

Hence, these formulae and the requisite for serine protease activity provide more than simply the name of a gene and satisfy the standard set in Eli Lilly.

With respect to the requirement for serine protease activity in the instant claims, the Federal Circuit in clarifying the holding of Eli Lilly stated "...Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003). As explained below in further detail, it was well-known in the art that the presence of a catalytic triad in a polypeptide retains protease activity. Hence, the function of serine protease activity is sufficiently correlated to a disclosed structure in MTSP7, the catalytic triad. Furthermore, specifying that the resulting polypeptides have serine protease activity is not a functional limitation, but is a constraint on the structure of the polypeptides.

The Office Action also alleges that because Applicant has not provided specific locations where amino acid changes may be made in MTSP7 polypeptide, the Applicant has failed to show identified structural features that permit recognition of the substrate. Applicant respectfully disagrees. The claims recite that the polypeptides possess serine protease activity. The specification identifies the catalytic triad as the amino acids that must be conserved for serine protease activity. The Examiner has provided no support for the assertion that the preservation of the catalytic triad is not sufficient for retaining serine protease activity in the instantly claimed polypeptides. The Examiner had provided no support to doubt the statements of the specification which state that polypeptides retaining at least about 80% and 90% identity to MTSP7 polypeptide sequences retain protease activity. Applicant has claimed polypeptides possessing serine protease activity, not a more particular substrate specificity. Therefore, the application identifies sufficient structural features of MTSP7 polypeptides to evidence possession of the claimed subject matter at the time of filing.

2. The specification provides additional relevant identifying characteristics of MTSP7 polypeptides

Although as noted above, the identification of sequence identity and serine protease activity are sufficient identifying characteristics to evidence possession of the claimed genus

of polypeptides, Applicant submits that the specification provides additional features that further evidence Applicant's possession of the claimed genus.

As discussed in the previous Response (mailed June 17, 2004), the specification describes additional identifying structural and functional characteristics of MTSP7 polypeptides. MTSP7 is a member of the transmembrane serine protease (MTSP) family of polypeptides The specification provides detailed description of conserved MTSP structural features (see for example, page 6, lines 14-20): The specification also delineates such features in the exemplary MTSP7 polypeptides provided (see for example, page 47, lines 4-15). The specification describes both single chain and two chain forms of MTSP7 polypeptides. The specification discloses that the protease domain of MTSP7 can be produced by cleavage at the (R↓I) site, producing an N-terminal sequence IVNG in the protease domain (page 49, lines 6-8). The specification describes that the protease domain can be produced by activated cleavage by catalysis or autocatalysis or (page 21, lines 7-10). The specification also identifies structural features in MTSP7 in single chain and two chain forms. For example, MTSP7 polypeptides have disulfide bond pairing between cysteines between positions Cys_{233} to Cys_{249}; Cys_{358} to Cys_{374}; Cys_{385} to Cys_{413} and Cys_{186} to Cys_{313} (page 51, line 28 to page 52, line 3) The specification further discloses that Cys_{313} is in the protease domain and is unpaired in the single chain form of the protease domain. Hence, the specification provides a number of structural features which identify MTSP7 polypeptides in addition to sequence identity with the exemplary SEQ ID NOS: 16 and 18 and the catalytic triad.

The specification also discloses different forms of MTSP7 polypeptides, including variants in polypeptide size that retain catalytic activity. The specification describes single chain and two chain forms of the polypeptide have catalytic activity (page 47, lines 11-15; see also Example 2). The specification provides polypeptides that include the MTSP7 protease domain or a catalytically active portion of the domain but do not include a full-length MTSP7 polypeptide. For example, the specification describes polypeptides that include the MTSP7 protease domain and can contain other non-MTSP sequences of amino acids but will include the protease domain or a sufficient portion for catalytic activity (page 49 lines 23-27). In another example, the specification discloses that the protease domain can be cleaved from a full length MTSP7 polypeptide by autocatalysis, by addition of a protease

or generated without activation (see for example, page 49, lines 1-8). The specification also exemplifies the expression, purification and activity of an MTSP7 protease domain in the Examples. Example 1 describes the cloning of an MTSP7 protease domain. Example 2 further describes the expression of an MTSP7 protease domain and purification of the polypeptide. Example 3 describes protease activity, substrates and assays with an MTSP7 protease domain.

The specification describes and exemplifies variation in MTSP7 polypeptides. The specification describes substantially purified polypeptides that have at least 80% and 90% identity with the exemplary MTSP7 polypeptides provided. The application further describes amino acid variations that can occur and/or be introduced into MTSP7 polypeptides. For example, the specification describes the substitution of functionally equivalent amino acid residues that result in a silent change (page 50, line 14 – page 51, line 10). The specification further describes groups of amino acids that can be interchanged (page 51, lines 11-16). The specification also contemplates non-conservative amino acids (page 53, lines 1-11). The specification exemplifies variation in the MTSP7 sequence. For example, the specification describes that the activation cleavage site can include variations such as R↓VVGG, R↓IVGG, R↓IVQ, R↓IVNG, R↓ILGG, R↓VGLL, R↓ILGG (page 49, lines 1-8) and non-conservative changes to the cleavage site by replacing a basic residue with a non-basic residue (page 53, lines 5-7). The specification also describes variants which replace cysteine residues in MTSP7. The specification describes exemplary replacements of Cys_{313} with serine, alanine and glycine (page 51, line 31 to page 52, line 3 and Example 3).

Thus, as described above, the specification describes and exemplifies variation in MTSP7 sequences commensurate with the polypeptides as claimed. Further, the specification provides structural characteristics and functional characteristics coupled with known and/or disclosed correlation with structural characteristics for such polypeptides. Therefore, Applicant has more than met the standard sufficient to demonstrate that the applicant was in possession of the claimed genus of MTSP7 polypeptides at the time of filing the application.

3. Serine Proteases and Serine Protease Structure-Function were well-known in the art

The standard for evaluating written descriptive is objective, based on what one of skill in the art would recognize in the disclosure. In re Gosteli, 872 F.2d at 1012. Hence,

evaluation of written description takes into account the knowledge of one of skill in the art with regard to the particular subject matter.

As discussed above, MTSP7 polypeptides are members of the serine protease family of proteins, in particular, transmembrane serine proteases. Serine proteases are well-recognized proteins. In fact, these proteins have distinct three-dimension structures and structural features that are readily distinguished. Many of the structural features of MTSP7 protease domains are conserved with other serine proteases (see for example, Hooper *et al.* (2001) J. Biol. Chem. 276:857-860and Lin *et al.* (1999) *J. Biol. Chem. 274*:18231-18236 as well as the references cited in the previous Response, mailed June 17, 2004). In addition, as explained by Pearson *et al.* ((1997) *Cabios Invited Review 13(4)*: 325-32), trypsin-like serine proteases share not just one but several diagnostic motifs throughout the protein. In addition to the catalytic triad, they share a conserved protein fold structure and antiparallel β barrels. The paper explains that using similarity to these multiple distinct motifs and structures, one of skill in the art can readily discern related proteins that have the same protein fold structure and protease activity.

Also known in the art were correlations between conserved features and structure-function relationships of serine proteases. For example, it was known in the art that the catalytic triad is necessary for catalytic activity. Further, it was known that residues surrounding the catalytic triad such as in the specificity pocket, influence proteolytic specificity and activity (see for example, Carter *et al.* (1988) *Nature 332:*564-68. Sprang *et al.* (1987) Science 237:905-09, Craik *et al.* (1987) Science 237:909-13 and Bachovchin *et al.* (1981) *Proc. Natl Acad. Sci. 78*: 7323-26). Hence, the requisites for retention of serine protease activity were well-known in the art.

At the time of filing one of skill in the art was familiar with variations that could be made in serine proteases. Such knowledge in the art included locations and types of amino acid substitutions that could be made in the protease domain. For example, Atwell *et al.* ((1999) *Proc. Natl. Acad. Sci. USA 96*:9497-9502) describes mutagenesis of subtiligase, an engineered subtilisin that retains the catalytic triad and oxyanion hole. Wells *et al.* (1987) *Proc. Natl. Acad. Sci. 84:*1219-23, describes the use of known information of serine protease-substrate contacts to design mutations in subtilisin. Additionally, with respect to trypsin-like serine proteases, Cheah *et al.* ((1990) *J. Biol. Chem. 265*:7180-7187) describes the use of

known structural and functional information about trypsin-like serine proteases to obtain mutations in a rhinovirus 3C protease with predicted functional phenotypes. Thus, at the time of the effective filing date of the claims at issue, one of skill in the art recognized the high level of conservation of structural and functional relationships among serine proteases and the structural requisites for activity. In view of this knowledge and the sequences of the MTSP7 provided in the application, applicant had possession of polypeptides that have the requisite sequence identity and retain serine protease activity.

4. One of skill in the art would recognize Applicant's possession of the claimed subject matter

To satisfy the written description requirement, the issue is not whether the specification literally listed all of the possible amino acid variant MTSP7 polypeptides that fall within the scope of the claims, but whether one of skill in the art in view of the specification would recognize polypeptide variants that have at least about 80% or 90% identity to the MTSP7 sequences and have serine protease activity, given the disclosure of the instant application.

In recognizing such variants, relevant structural and functional identifying characteristics can be sufficient to provide one of skill in the art the necessary written description. See, Eli Lilly, 119 F. 3d at 1568. As noted above, the application provides relevant structural and functional features that identify the claimed genus of polypeptides. Such features include exemplary amino acid sequences of MTSP7 polypeptides and protease domains, delineation of the boundaries of the protease domain, identifying structural features in the protease domain including the catalytic triad and correlations of function with such structural features. Hence, the instant application provides numerous relevant structural and functional identifying characteristics of MTSP7 polypeptides such that one of skill in the art could recognize claimed MTSP7 polypeptides and variants.

In addition, the standard for evaluating written description is based on the knowledge of skill in the art. In re Gosteli, 872 F.2d at 1012. As discussed in detail, above, with respect to serine proteases, the knowledge of one of skill in the art was very high at the time of filing and before. Serine proteases are a highly conserved family of proteins with demonstrated structure-function correlations. Serine proteases have a highly conserved three dimensional structure and a number of highly conserved distinguishing motifs through out the protein. As

evidenced by the literature, structure-function correlations for serine proteases also were known in the art..

Therefore, in light of Applicant's disclosure, one of skill in the art would have recognized from reading the application, that Applicant provided MTSP7 polypeptides with the sequences set forth in SEQ ID NOS: 16 and 18 and polypeptides with variations in these sequences in regions of the polypeptides such that the polypeptides would possess serine protease activity. Given the conserved features of serine proteases identified in the application and known in the art, coupled with the ability to test for functional variants using assays provided in the application, one of skill in the art would recognize that Applicant was in possession of the claimed subject matter at the time of filing of the application. Therefore, Applicant respectfully requests that the rejection be withdrawn.

B. The enablement rejection of claims 1, 2, 4-6, 9, 10, 18, 19, 50-55, 59-61, 65-67, and 68-72

Claims 1, 2, 4-6, 9, 10, 18, 19, 50-55, 59-61, 65-67, and 68-72 are rejected for lack of enablement because the specification is not enabling for any embodiment of a polypeptide comprising an MTSP7 protease domain that has an amino acid sequence diverging from SEQ ID NO:18 by as many as 23 amino acids or diverging from SEQ ID NO:16 by as many as 44 amino acids. It is alleged that the specification does not show how or where such amino acid variation should be made in SEQ ID NOS:16 and 18. The Final Office Action contends that because the prior art does not identify proteins having a 10% sequence divergence and maintaining catalytic activity, it would be unpredictable how to make such changes in MTSP7 polypeptides and maintain activity. Reconsideration and withdrawal of the rejection are respectfully requested.

Relevant Law

To satisfy the enablement requirement of 35 U.S.C §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Application of the Factors Enumerated in In re Wands

As discussed in detailed below as well as enumerated in more detail in the previous Response (mailed June 14, 2004, referred hereinafter as "Response"), a consideration of the factor enumerated in In re Wands demonstrates that the application, in conjunction with what was known to one of skill in the art, teaches how to make and use the subject matter as claimed. It would not require undue experimentation to make and use polypeptides as claimed, including polypeptides with at least about 90% identity with sequences of the polypeptide set forth in SEQ ID NOs. 16 and 18. Although claims reciting at least about 80% identity with MTSP7 sequences are not rejected by the instant Office Action, Applicant respectfully submits that the analysis herein is equally applicable to such claims; it also would not require undue experimentation to make and use with at least about 80% identity with polypeptide sequences as set forth in SEQ ID NOs. 16 and 18 as instantly claimed

Breadth of the Claims

Claims 1, 2, 4-6, 9, 10, 18, 19, 50-55, 59-61, 65-67, and 68-72 are described above with respect to the written description rejection.

Level of Skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

Teachings of the Specification

The specification provides all of the necessary guidance for one of skill in the art to make and use polypeptides with the claimed variation. The Response provided an extensive discussion of the teachings of the specification that is summarized herein. First, the specification provides the amino acid sequences, *i.e.* the chemical structures of MTSP7 polypeptides as set forth in SEQ ID NOS: 16 and 18. Second, the specification delineates the catalytic region of MTSP7 polypeptides, including providing a representative protease domain amino acid sequence and identification of the boundaries of the domain in the full length polypeptide sequence. Third, the specification identifies structural features that contribute to catalytic activity such as the catalytic triad, oxyanion hole and primary specificity pocket. Additionally, the specification teaches that these features are conserved in well known serine proteases in the art. The specification identifies additional features that contribute to the structure of the protein, including free cysteines and cysteines that participate in disulfide bonding and protease cleavage sites at the N-terminal region of the protease domain. Fourth, having identified for one of ordinary skill in the art relevant regions of the protein for serine protease activity, the specification provides exemplary serine protease assays that can be used to confirm protease activity. Hence, the specification provides one of ordinary skill in the art with all of the necessary materials and guidance: chemical structures, relevant structural and functional regions for activity, and assays for serine protease activity.

Knowledge of those of skill in the art

At the timing of filing of the application and before, those of skill in the art were very familiar with serine proteases generally, including sequence and structure of a number of polypeptide members of the serine protease family. As is noted herein and discussed in the previous response, there is a large body of literature directed to serine proteases. Those of skill in the art were very familiar with serine proteases generally, including sequence and structure of a number of polypeptide members of the serine protease family at the time of filing and before. There was a large body of literature directed to serine proteases and there was general understanding of their structures and requisites for activity. This is evidenced, for example, in the application and in literature made of record in the Information Disclosure Statements submitted. As noted in the application, a large number of Type II Serine

Proteases (TTSPs), also referred to as MTSPs, were known (see for example, page 3, at line 14 to page 4, line 11). In addition, a large body of knowledge was available for the large protein family of serine proteases. (see for example, Hooper *et al. J. Biol. Chem. 276*:857-860, Nienaber *et al.* (2000) *J. Biol. Chem.* 275:7239-48; Sommerhoff *et al.* (1999) *Proc. Natl. Acad. Sci. USA* 96:10984-91; Lu *et al.* (1999) J. Mol. Biol. 292:361-73; Xu *et al.* (2000) *J. Biol. Chem.* 275:378-385, Lin et al.(1999) *J. Biol. Chem. 274*: 18231-36 and Bryan (2000) *Biochem. Biophys. Acta 1543*:200-03, cited and discussed in the previous response). These references detail the existing crystal structures, structural comparisons and structural similarities of serine proteases. Hence, a wide variety of structural information on serine proteases was well-known in the art. The references emphasize that the presence of a catalytic triad in the protease confers serine protease activity.

The methods and guidance for comparing amino acid sequences to generate and confirm sequences with at least 90% identity to a polypeptide sequence such as SEQ ID NOS: 16 and 18 was available in the art at the time of filing. As described in the instant specification computer algorithms such as the "FAST A" program, using for example, the default parameters as in Pearson et al. (1988) Proc. Natl. Acad. Sci. USA 85:2444 (other programs include the GCG program package (Devereux, J., *et al.* , Nucleic Acids Research 12(I):387 (1984)), BLASTP, BLASTN, FASTA (Atschul, S.F., *et al.* , J Molec Biol 215:403 (1990); Guide to Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo et al. (1988) SIAM J Applied Math 48:1073) were available. In addition, as discussed in the previous response, methods for generating nucleotide and protein sequence variation were widely available in the art. Thus, one of skill in the art could use such programs with a serine protease sequence, for example, to align the sequence and identify the structural features of importance for retention of activity and use the methods for generating sequence variation to make the identified protein variants.

Methods for assaying protease activity including protease specificity, level of activity and response to inhibitors was well known in the art (see, for example, Lu *et al.* (1999) J. Mol. Biol. 292:361-73; Xu *et al.* (2000) *J. Biol. Chem.* 275:378-385). Methods for high throughput assays and detection were also widely available (See generally, *High Throughput Screening: The Discovery of Bioactive Substance*s (Devlin, Ed.) Marcel Dekker, 1997; Sittampalam *et al., Curr. Opin. Chem. Biol.*, 1:384-91 (1997); and Silverman *et al., Curr.*

Opin. Chem. Biol., 2:397-403 (1998)). Hence, the amount of knowledge of those of skill in the art was extensive and the requisite structural and functional features required for protease activity was well known.

Working Examples

The specification provides working examples that exemplify MTSP7 polypeptides, protease domains and variants. Example 1 exemplifies the cloning of MTSP7 protease domain and full-length MTSP7 polypeptides and teaches the conserved sequences of MTSP7 polypeptides with other known serine proteases. Example 2 exemplifies mutagenesis of an MTSP7 protease domain polypeptide to replace Cys_{313} with a serine. Example 2 further demonstrates the expression and purification of an isolated protease domain, in the absence of cleavage and activation from the full-length form. Example 3 teaches serine protease assays. Example 4 exemplifies additional serine protease assays, including assays for specificity and comparison with other serine. In summary, the examples provide a teaching of all of the steps one of skill in the art would need to make and use additional MTSP7 polypeptide variants.

Predictability

The predictability at issue herein is whether one of skill in the art could predictably make polypeptides that had at least about 90% identity with the recited sequences as claimed, and whether such polypeptides would possess serine protease activity. In each case, the answer is yes, one of skill in the art given the instant disclosure could predictably make such polypeptide variants with serine protease activity.

In contrast to the allegations of "unpredictability" set forth in the Final Office Action, the specification and the knowledge in the art evidence many factors of ***predictability*** with respect to MTSP7 polypeptide variants. First, the specification provides exemplary polypeptides. These are defined chemical structures from which one of skill in the art is given a reference point. Second, the specification delineates structural and functional features of the protein. These features identify key regions and residues that one of skill in the art would know to conserve in order to retain serine protease activity. These features also provide reference points for alignments with other known serine proteases. These features also allow one of skill in the art to make further structure-function correlations, again providing predictable correlations of regions and residues to conserve or change. As

evidenced by the plethora of references cited in the specification and in the Information Disclosure Statements of record in this application, a large body of knowledge pertain to structure-function relationships of serine proteases was known in the art. In addition, the specification provides exemplary assays to assay serine protease activity. Additional assays were available in the art. One of skill in the art could readily and routinely test any MTSP7 variant for serine protease activity.

Additionally, as noted above with respect to the written description rejection, the instant claims are drawn to polypeptides with serine protease activity, not a more particular substrate activity. Hence, all that is needed is an enabling disclosure of how to make a serine protease that has at least about 90% identity with the provided polypeptide sequences that retains serine protease activity. As taught in the specification as well as evidenced by the art of record, maintenance of the catalytic triad is sufficient to retain serine protease activity. Therefore, one of skill in the art could make and generate variants of MTSP7 polypeptides with at least about 90% identity to the exemplary MTSP7 polypeptide sequences provided in the application that also preserve the catalytic triad. Serine protease activity of these variants could easily and routinely be confirmed using the assays provided in the application and known in the art. The routine manipulations to generate an MTSP7 variant, *e.g.* selecting non-catalytic triad residues and aligning variant sequences to confirm at least about 90% identity are not unpredictable.

Conclusion

In light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, the fact that it is predictable to make variations in MTSP7 polypeptides and protease domains using the guidance of the specification, and the breadth of the claims, it would not require undue experimentation for one of skill in the art to make and use polypeptides with variations in SEQ ID NOs. 16 and 18 as claimed. Accordingly, a consideration of the factors enumerated above leads to the conclusion that, based on the disclosure in the specification, undue experimentation would not be required to make and use polypeptides as instantly claimed. Therefore, Applicant respectfully requests withdrawal of the rejection.

"Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be

undue experimentation. '***The key word is undue, not experimentation.***' " In re Wands, 858 F.2d at 737-38 (quoting In re Angstadt, 537 F.2d at 504; emphasis added; additional internal citations omitted). The experimentation necessary to make and use MTSP7 variants, as described above, is routine; it is not undue.

The art related to serine proteases demonstrates that such experimentation is not undue. For example, Pearson *et al.* ((1997) *Cabios Invited Review 13(4)*: 325-32) explains that serine proteases share a conserved catalytic site, the catalytic triad. In addition, trypsin-like serine proteases have several diagnostic motifs throughout the protein including a conserved protein fold and anti-parallel β barrels structure that contributes to the function of the protease. Pearson *et al.* states that one could recognize proteins that have protease activity based on these conserved structures. Hence, generation of variants with serine protease activity is routine because one of skill in the art can use such conserved features as a guide for designing the location of variations to maintain these features. In addition, Cheah *et al.* ((1990) *J. Biol. Chem. 265*:7180-7187) provides a demonstration of the predictability of generating variants of serine proteases based on an exemplary sequence. The authors use known structural and functional information about trypsin-like serine proteases to obtain mutations in a rhinovirus 3C protease with predicted functional phenotypes. Thus, the art available at the time of filing and before demonstrates that one of skill in the art could make variants of a serine protease in a predictable manner.

Comments with respect to specific points raised in the Office Action

Notwithstanding the arguments above demonstrating that the specification is enabling for the claimed subject matter, Applicant wishes to address specific issues raised in the Office Action.

1. The Final Office Action alleges that making multiple mutations in a serine protease would be unpredictable, but no supporting evidence for such allegation is provided. Applicant has provided numerous references available in the art at and before the effective filing date of the claims at issued. These references evidence the numerous mutations that have been made in proteins belonging to the larger family of serine proteases. The references demonstrate that using structure-function correlations for serine proteases, one of skill in the art could make variants of serine proteases that retain serine protease activity. Although the Office Action further alleges that if multiple mutations are made or combined, the art

becomes "unpredictable," no supporting documentation for such allegation has been provided. Applicant is not aware of any references of record that would indicate that making multiple amino acid changes in a serine protease is an unpredictable art. To the contrary, references such as Pearson *et al.* ((1997) *Cabios Invited Review 13(4)*: 325-32, supra) evidence that trypsin-like serine proteases, although encompassing a wide variety of sequences, retain conserved structural features and serine protease activity. Hence, the family of proteins is tolerant to a wide variation of polypeptide sequences. Therefore, Applicant respectfully requests that the Examiner provide supporting documentation for any allegations that making multiple mutations in serine proteases would be unpredictable.

2. The Office Action alleges that the Bryan reference lends no support to the argument that MTSP7 and other serine proteases are highly tolerant to mutation because subtilisin is not a type II serine protease. Although subtilisin is not a mammalian type II serine proteases, such proteins are members of the larger family of serine proteases. Hence, subtilisin is still a model for the serine protease family. As noted Bryan describes that over half of the amino acids in subtilisin have been mutated. The reference demonstrates that for subtilisin as a model serine protease, the data on mutagenesis exists for over half the residues of the protein. Furthermore, although the Examiner alleges that the progress in subitlisin has been incremental over the past 25 years, this comment misses the point of Bryan. The reference evidences the compilation of data that has been generated and was available at or before the effective filing date of the claims at issue. Bryan demonstrates that a large collection of structure-function data for a serine protease were available to one of skill in the art at the time of the effective filing date of the claims at issue. The rate at which such data was obtained is irrelevant; the pertinent issue is what was available to one of skill in the art at the time of filing.

3. The Examiner alleges that "Applicant cannot point to any teaching in the specification of the nature of such extensive alterations that might result in a variant to [sic] that will function as a protease." Applicant respectfully submits that the specification does so teach . The specification states that the catalytic triad of the protease domain is necessary for serine protease activity. Furthermore, the specification states that polypeptides that contain at least about 90% identity with the exemplary sequences provided therein possess catalytic activity. Applicant respectfully submits that no other structural features are required to make

and use the claimed polypeptides. The Examiner has provided no supporting evidence to doubt the veracity of the specification. Applicant has provided numerous references (see for example, Carter *et al.* (1988) *Nature 332:*564-68. Sprang *et al.* (1987) Science 237:905-09, Craik *et al.* (1987) Science 237:909-13 and Bachovchin *et al.* (1981) *Proc. Natl Acad. Sci. 78*: 7323-26) that evidence the requirement of the catalytic triad for catalytic activity. Therefore, the application provides all of the necessary guidance for making the claimed polypeptides.

IV. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112, Second Paragraph

The Office Action alleges that claims 4, 6, 52-55, 69, 117 and 118 are indefinite due to the recitation of "portion" multiple times in claim 4, where a portion allegedly can include another portion. Claims 6, 52-55, 69 and 177-118 are included in the rejection because they depend from claim 4.

Claim 4 as amended herein recites:$$

> 4. A substantially purified single or two chain polypeptide, comprising an MTSP7 portion, wherein:
> said MTSP7 portion is the only MTSP7 portion of the single or two chain polypeptide and is a protease domain of MTSP7 selected from the group consisting of
> a) a polypeptide consisting essentially of the sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17;
> b) a polypeptide consisting essentially of the sequence of amino acids that has at least about 90% amino acid sequence identity with the sequence of amino acids set forth as SEQ ID No. 18; and
> c) a polypeptide that is a **catalytically active portion** of a) or b);
> and the MTSP7 portion of the polypeptide has serine protease activity.

It is clear from the context of the claims and the other language to what each recitation of portion refers. There is "MTSP7 portion" and a "catalytically active portion;" that are different. The claim recite proper antecedent for each different portion. In particular, claim 4 recites an "MTSP7 portion" (underlined above). An MTSP7 portion is defined in the specification and the claim as a protease domain of MTSP7. Claim 4 further specifies that the protease domain is one of the polypeptides as listed in a), b) and c) of the claim. Alternative "c)" of claim 4 recites that the protease domain is a polypeptide that is a catalytically active portion of alternatives "a) or b)." The claim language clarifies that this second use of the term portion refers to one that is a smaller region of the protease domain as set forth in alternatives "a)" and "b)"and it is catalytically active. Hence, although the word

"portion" is used more than once in the claim language, the claim distinguishes the different portions by the terms "MTSP7 portion" and "catalytically active portion of a) or b)" The claim also recites that the specified MTSP7 portion is the only MTSP7 portion of the polypeptide, thereby clearly excluding full-length MTSP7 molecules from its scope. Applicant respectfully submits that claim 4 and claims dependent thereon are definite and therefore, respectfully requests withdrawal of the rejection.

V. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §102(e)(1)

Claims 4, 6, 52-55, 69, 120 and 122 are rejected under 35 U.S.C. §102(e)(1) as being anticipated by Alsobrook *et al.* (U.S. Patent Application No. 2003/0170630) because the human serine protease disclosed by Alsobrook *et al.* allegedly is identical to SEQ ID NO:18 and meets the limitation of clause (b) of claim 4 and claim 6 dependent thereon. It is further alleged that Alsobrook *et al.* discloses conjugates, attachment to surfaces and screening methods such as claimed in claims 52-55 and 69. Additionally, the Office Action alleges that Alsobrook *et al.* inherently anticipates claims 120 and 122 because it discloses recombinant expression of proteases in eukaryotic cells that would allegedly result in activated cleavage and a two-chain protease. Reconsideration and withdrawal of these rejections are respectfully requested in view of the clarification of the claim language herein and the following remarks.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the

art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the "'prior art'" . . .the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). In re Arkey, Eardly, and Long, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

The Claims

Claim 4 is directed to a substantially purified single or two chain polypeptide comprising an MTSP7 portion. Claim 4 specifies that the MTSP7 portion is a protease domain of MTSP7 and the specified MTSP7 portion is the only MTSP7portion of the polypeptide, so that the claimed polypeptide cannot and does not read on a full-length MTSP7 polypeptide. Claim 4 further specifies that the protease domain is selected from the group consisting of a) a polypeptide consisting essentially of the sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17; b) a polypeptide consisting essentially of the sequence of amino acids that has at least about 90% amino acid sequence identity with the sequence of amino acids set forth as SEQ ID No. 18 and c) a polypeptide that is a catalytically active portion of a) or b). The MTSP7 portion of the polypeptide has serine protease activity.

Claims 6, 52-55 and 69 depend from claim 4. Claim 6 is directed to the polypeptide of Claim 4 that contains an N-terminal cleavage site or activated cleavage site and a catalytic triad of His, Asp and Ser residues. Claims 52 and 54 are directed to conjugates containing a polypeptide of claim 4 or claim 6, respectively, and a targeting agent linked to the polypeptide directly or via a linker. Claims 53 and 55 specify particular characteristics of the targeting agent that is an element of claims 52 and 54. Claim 69 is directed to a method for

identifying compounds that modulate the protease activity of a polypeptide by contacting the polypeptide of Claim 4 with a substrate and either simultaneously, before or after, adding one or more test compounds, measuring the amount of substrate cleaved in the presence of the test compound and selecting compounds that change the amount of substrate cleaved compared to a control so that compounds that modulate the activity of the polypeptide are identified. Claim 69 further specifies that the identified compounds inhibit tumorogenesis.

Claims 120 is directed to a substantially purified activated two chain polypeptide, comprising the protease domain of MTSP7 or a catalytically active portion thereof where the polypeptide has at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 18 and the polypeptide has serine protease activity. Claim 122 is directed to a substantially purified one or two chain polypeptides that consists essentially of the protease domain of MTSP7 or a catalytically active portion thereof where the protease domain or catalytically active portion thereof has at least about 80% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 18.

Alsobrook *et al.*

Alsobrook *et al.* discloses a polypeptide have a sequence, set forth as SEQ ID NO:2 therein, that is 420 amino acids in length. The polypeptide disclosed by Alsobrook *et al.* shares regions of identity with SEQ ID NO:18 of the instant application but it is not identical to SEQ ID NO:18. SEQ ID NO:2 disclosed by Alsobrook *et al.* contains 2 amino acids differences in the protease domain from Sequence ID NO:18. Additionally and significantly, the polypeptide disclosed by Alsobrook *et al.* contains an additional 184 amino acids compared to the polypeptide that has the sequence of SEQ ID NO:18 and the polypeptides as claimed.

ANALYSIS

Claim 4 and claims dependent thereon

Claim 4 and claims dependent thereon are directed to polypeptides that contain MTSP7 protease domain and that the only MTSP7 portion of the polypeptides is a protease domain of MTSP7 as set forth in alternatives a), b) and c) listed therein.

Claim 4 does not encompass full-length MTSP7 proteins, nor polypeptides that contain additional regions of MTSP7 other than the protease domain. The claim recites that said MTSP7 portion is the only MTSP7 portion of the single or two chain polypeptide and that

said MTSP7 portion is a protease domain of MTSP7. Further, the claim defines the protease domain as either a) a polypeptide consisting essentially of the sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17; b) a polypeptide consisting essentially of the sequence of amino acids that has at least about 90% amino acid sequence identity with the sequence of amino acids set forth as SEQ ID No. 18 and c) a polypeptide that is a catalytically active portion of a) or b). Hence, the only MTSP7 sequences within the claimed polypeptides are these specified regions or a smaller region (a catalytically active portion of these sequences). Therefore, polypeptides that contain other regions of identity with MTSP7, such as regions N-terminal to the protease domain of MTSP7, are not encompassed by claim 4.

Alsobrook *et al.* does not disclose any substantially purified single or two chain polypeptides where the only MTSP7 portion is an MTSP7 protease domain as recited in claim 4. Although SEQ ID No. 2 disclosed in Alsobrook *et al.* has a region of identity with SEQ ID No. 18, this portion is not the only MTSP7 portion in the polypeptide; the polypeptide contains a protease domain **and** an additional 184 amino acids. Further, the additional amino acids as set forth in SEQ ID NO:2 disclosed by Alsobrook *et al.* contains regions of identity with MTSP7 polypeptides such as SEQ ID No. 18 disclosed in the instant application. For example, amino acids 79-100 and amino acids 142 to 182 of SEQ ID NO:2 disclosed by Alsobrook *et al.* are nearly or completely identical to portions of SEQ ID NO:18. Hence, SEQ ID NO:2 contains additional portions of MTSP7 polypeptide sequence beyond the protease domain. Therefore, SEQ ID NO:2 is not a polypeptide where the only MTSP7 portion of the polypeptide is an MTSP7 protease domain as instantly claimed.

Since anticipation requires that a reference disclose every element of a claim, Alsobrook *et al.*, which does not disclose a substantially purified single or two-chain polypeptide where the only MTSP7 portion of the polypeptide is a protease domain of MTSP7 selected from a) a polypeptide consisting essentially of the sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17; b) a polypeptide consisting essentially of the sequence of amino acids that has at least about 90% amino acid sequence identity with the sequence of amino acids set forth as SEQ ID No. 18 and c) a polypeptide that is a catalytically active portion of a) or b), does not disclose very element of

claim 4. Therefore, the reference does not anticipate the claim 4 or any claims dependent thereon.

Claim 120

Alsobrook *et al.* also does not anticipate claim 120, which is directed to activated two chain polypeptides that comprise the protease domain of MTSP7 or a catalytically active portion thereof with at least 90% identity to SEQ ID NO:18 and that have serine protease activity. Alsobrook *et al.* does not disclose *any* two chain polypeptides. Alsobrook *et al.* discloses a linear sequence of amino acids, sequence SEQ ID NO:2 therein. Alsobrook *et al.* does not disclose any cleavage of SEQ ID NO:2, nor any disulfide bridging, nor any other such interactions of the linear SEQ ID NO:2 that would create a two chain polypeptide. Alsobrook *et al.* does not disclose purification of any two chain polypeptides.

The Examiner alleges that Alsobrook *et al.* inherently discloses a two chain polypeptide because it discloses recombinant expression of the polypeptide. Applicant respectfully disagrees. The Examiner has provided no substantiating evidence that a substantially purified activated two chain polypeptide is an inherent property of expression of the polypeptide disclosed by Alsobrook *et al.* Applicant respectfully submits that a substantially purified activated two chain polypeptide is not an inherent property thereof. An inherent property has to flow naturally from what is taught in a reference. In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981). "The fact that a certain result may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP § 2112 (citing In re Rijckaert, 9 F.3d 1531, 1543 (Fed. Cir. 1993) (emphasis in the original). The claims recite "a substantially purified activated two chain polypeptide," the combination of these features is not an inherent characteristic that naturally flows from what is taught by Alsobrook *et al.*. Further, Alsobrook *et al.* does not disclose purification of activated two chain polypeptides.

First, an "activated two chain polypeptide" specifies that the polypeptide is in a two-chain form. A two-chain form, as explain in the specification, contains the two chains of the polypeptide associated by disulfide bonds between cysteines. Disulfide bonds are not inherent in proteins. Dependent upon the conditions such as the pH, and presence of reducing or oxidizing agents, disulfide bonding may be present. Hence, depending on its surrounding environment, *e.g.*, how the polypeptide is synthesized and/or substantially

purified, it may not be in a two-chain form. Therefore, a two-chain form is not an inherent characteristic.

Second, "substantially purified" also is not an inherent characteristic. To produce a substantially purified form of a protein where more than one form of the protein is possible, it must be produced only in one form, exclusive of the other forms or it must purified from the mixture of forms. As explained in the instant specification, MTSP7 polypeptides can occur in several forms including single and two-chain forms, forms with and without disulfide bridges and forms that have been activated through cleavage. The instant specification also discloses that cell types can vary in the levels of activated and non-activated forms. Hence, without further manipulations, expression of an MTSP7 polypeptide does not result in a substantially purified activated two chain form. Therefore, a substantially purified activated two-chain form is not an inherent characteristic of an MTSP7 polypeptide.

Alsobrook *et al.* provides no disclosure of a substantially purified activated two-chain polypeptide as claimed. As discussed above, such features are not inherent to the polypeptide sequences disclosed by Alsobrook *et al.*, nor to the expression of such polypeptide sequences. Second, Alsobrook *et al.* provides no additional disclosure that evidence preparation of a substantially purified activated two-chain. Although Alsobrook *et al.* discloses recombinant expression of polypeptides, it does not disclose any expression systems that generate a substantially purified activated two-chain form, nor any methods of substantially purifying a two-chain form from the mixture of possible polypeptide forms that could be produced. Alsobrook *et al.* does not even disclose that a two-chain form exists. As noted above, "[t]he fact that a certain result may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP § 2112 (citing In re Rijckaert, 9 F.3d 1531, 1543 (Fed. Cir. 1993) (emphasis in the original)). Thus, even if some proportion of the polypeptide sequence disclosed by Alsobrook *et al.* is recombinantly expressed, and even if some of the expressed polypeptide can be cleaved into two chains, and even if some proportion of the cleaved polypeptide chains can be associated by disulfide bonds, such possibilities upon possibilities do not result in a substantially purified activated two chain polypeptide.

Thus, Alsobrook *et al.* does not explicitly or inherently disclose *any* substantially purified activated two chain polypeptides. Therefore, it does not disclose a substantially

purified activated two chain polypeptide containing the protease domain of an MTSP7 or a catalytically active portion thereof wherein the protease domain has at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID NO:18 as claimed. Hence, Alsobrook *et al.* does not anticipate claim 120.

Claim 122

Alsobrook *et al.* also does not anticipate claim 122 drawn to a substantially purified single or two chain polypeptide that consists essentially of the protease domain of MTSP7 or a catalytically active portion thereof wherein the protease domain has at least about 80% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID NO:18 and the polypeptide has serine protease activity.

First, Alsobrook *et al.* does not disclose any polypeptides that consist essentially of the protease domain of MTSP7 or a catalytically active portion of the protease domain. The polypeptides disclosed by Alsobrook *et al.*, SEQ ID NO:2, as explained above, contains additional portions of MTSP7, including an additional 184 amino acids beyond the protease domain. There is no disclosure by Alsobrook *et al.* of any polypeptides containing only the protease domain or a smaller fragment of the protease domain of an MTSP7 polypeptide.

Second, a polypeptide that consists essentially of the protease domain of MTSP7 or a catalytically active portion of the protease domain is not an inherent property of the polypeptide sequence disclosed by Alsobrook *et al.*, nor is it an inherent property of an MTSP7 polypeptide. As explained in the instant specification, MTSP7 polypeptides can be cleaved to yield a polypeptide that consists essentially of the protease domain. Such cleavage and the resulting polypeptide, however, is not an inherent property. The instant specification states that activated and non-activated forms of MTSP7 polypeptides can vary by cell type. Hence, in some cell types a cleaved form of MTSP7 can be present, whereas in other cell types MTSP7 is in the uncleaved form. As noted above, an inherent property has to flow naturally from what is taught in a reference. In re Oelrich, 666 F.2d at 581. Further, "[t]he fact that a certain result may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP § 2112 Alsobrook *et al.* offers no disclosure of cleaved forms of MTSP7, conditions for such cleavage, nor cell types in which such cleavage occurs. Hence, just because there is a possibility that some proportion of the polypeptide sequence disclosed by Alsobrook *et al.* may or could be cleaved, is not sufficient

to establish the inherency of a polypeptide that consists essentially of the protease domain of MTSP7.

Additionally, as discussed above, "substantially purified" is not an inherent characteristic. To produce a substantially purified form of a protein where more than one form of the protein is possible, it must be produced only in one form, exclusive of the other forms or it must purified from the mixture of forms. As explained in the instant specification, MTSP7 polypeptides can occur in several forms including single and two-chain forms, forms with and without disulfide bridges and forms that have been activated through cleavage. The instant specification also discloses that cell types can vary in the levels of activated and non-activated forms. Hence, without further manipulations, expression of an MTSP7 polypeptide does not result in a substantially purified form that consists essentially of the protease domain. Therefore, a *substantially purified* polypeptide that consists essentially of the protease domain is not an inherent characteristic of an MTSP7 polypeptide.

. Therefore, although Alsobrook *et al.* discloses recombinant expression of polypeptides, it does not inherently disclose any polypeptides that consist essentially of the protease domain of MTSP7 or a catalytically active portion thereof. Alsobrook *et al.* does not disclose any recombinant expression systems that inherently generate a substantially purified cleaved form of MTSP7, nor any methods of substantially purifying such form from the mixture of possible polypeptide forms that could be produced. Alsobrook *et al.* does not even recognize that a cleaved form consisting of the protease domain of the polypeptide could be produced. Hence, it does not disclose purification of a two chain form from other forms of the polypeptide.

Thus, Alsobrook *et al.* does not explicitly or inherently disclose *any* substantially purified activated two chain polypeptides. Therefore, it does not disclose a substantially purified activated two chain polypeptide consisting essentially of the protease domain of an MTSP7 or a catalytically active portion thereof that has at least about 80% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID NO:18 and has serine protease activity as claimed. Hence, Alsobrook *et al.* does not anticipate claim 122.

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In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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